Int. Journal of Math. Analysis, Vol. 7, 2013, no. 9, 413 - 424

Modeling Co-infection of Paediatric Malaria and Pneumonia

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Abstract

Malaria and persistent childhood diseases are a major threat to child survival in the developing world. In this paper, we develop and analyse a mathematical model for paediatric malaria and pneumonia co-infection. We establish the existence of equilibria points in terms of the basic reproduction numbers R_m and R_p. The analysis shows that the disease-free equilibrium of the model is globally asymptotically stable whenever the co-infection reproduction number R_{mp} is less than unity. Sensitivity analysis of the reproduction numbers show that an increase in the treatment rate results in an expected decline of new disease incidences.

Mathematics Subject Classification: 34D20

Keywords: Malaria-pneumonia model, Co-infection, Basic reproduction number, Stability

1 Introduction

Humans acquire malaria following infective bites from infected Anopheles female mosquitoes during blood feeding. *Plasmodium falciparum* is the parasite species that largely causes human malaria infections in Africa. Each year 350-500 million cases of malaria occur worldwide, and over one million people die,

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most of them young children less than five years of age in sub-Saharan Africa. Malaria was the fourth cause of death in children in developing countries in 2002. In Kenya it accounts for 19% of all hospital admissions, 30% of all outpatient visits, with an estimate of 20% of all deaths in children less than five years of age being attributed to the disease [4].

Many children living in malaria-endemic areas are frequently exposed to other diseases such as pneumonia. Pneumonia is an air-bone respiratory disease caused by infection inside the lungs. It may be contracted by breathing in droplets containing disease causing organisms, released into air when an infected person coughs or sneezes. Pneumonia may also be contracted when bacteria or viruses that are normally present in the mouth, throat, or nose inadvertently enter the lung. The most common cause of bacterial pneumonia is *S. pneumoniae*. The symptoms of pneumonia include: cough, difficult breathing, fever, muscle aches, loss of appetite and lethargy. The risk factors for pneumonia include smoking and second-hand smoke, alcohol and drug abuse, crowded living conditions and certain medical conditions. These include conditions that interfere with the gag reflex, weaken the immune system and organ transplant. A weak immune system may be as a result of prolonged malaria exposure, malnutrition among other factors. Children have a higher risk of developing pneumonia if they have weakened immune systems. Statistics show that of all children outpatients suffering from respiratory complications, 25 percent of the cases are confirmed to be pneumonia. The Kenyan case is no different the percentage being 18. Pneumonia mortality in children is very high especially in the developing world, with an estimate of 5,500 deaths per day [6].

A study carried out in Uganda showed that 27 (19%) out of the 139 children enrolled in an urban hospital were co-infected with both malaria and pneumonia [1]. Another study carried out in Uganda also showed that out of 2,944 malaria cases in under-fives at 14 health centres, 37% had pneumonia [3]. The most common causes of deaths in Kenyan children after the neonatal period are pneumonia, diarrhoea, measles, malaria, and malnutrition or a combination of these conditions [5]. In this paper we explore the co-dynamics of malaria and pneumonia by formulating and analysing a mathematical co-infection model.

2 Model Description and Formulation

The total human population size N_H at any time is subdivided into the classes: susceptible S_H, infectious with malaria I_M, infectious with pneumonia I_P and symptomatically infectious with malaria and pneumonia I_{MP} . The human population is not assumed to be constant since birth, migration, emigration

and death occur. However we assume that the probability of survival till the infectious state for individuals exposed to malaria as well as those exposed to pneumonia is unity and therefore exclude the class of individuals exposed to these diseases. The constant per capita recruitment rate into the susceptible human population is Λ_H. The vector population N_V is subdivided into the susceptible S_V and infectious I_V classes. The constant per capita recruitment rate into the susceptible vector population is Λ_V. Let μ_H and μ_V be per capita natural death rates of the human and mosquito populations respectively.

Due to malaria related immunodeficiency we include the modification parameter ϑ to account for the increased susceptibility to infection with pneumonia. The human population suffer disease induced mortality at the rate σ. The expected decrease in contact due to ill health as a result of pneumonia disease is accounted for by the parameter $0 < \varepsilon < 1$. Movement back to the susceptible class upon recovery from the class I_{MP} is at the rate ϕ. Let the rate of recovery from I_P to S_H be τ, while that from I_M to S_H be π.

The rates of infection of susceptible humans with malaria and pneumonia are λ_M and λ_P respectively while that of susceptible vectors is λ_V. Define α as the number of bites per human per mosquito, β_m as the transmission probability of malaria in humans, β_v as the probability that a mosquito becomes infected with malaria from any infected human, β_p as the probability that one individual is being infected with pneumonia by one infectious individual and c is the per capita contact rate. This yields $\lambda_M = \frac{\alpha\beta_m I_V}{N_H}, \lambda_v = \frac{\alpha\beta_v(I_M+\delta I_{MP})}{N_H}$ and $\lambda_P = \frac{\beta_p c(I_P+\kappa I_{MP})}{N_H}$ as the forces of infection, where δ and κ are modification parameters accounting for the relative infectiousness of the co-infected individual as compared to their counterparts. From the above definitions and variables we have the following model with nonnegative initial conditions

$$\begin{aligned}
\frac{dS_H}{dt} &= \Lambda_H - \lambda_M S_H - \lambda_P S_H - \mu_H S_H + \pi I_M + \tau I_P + \phi I_{MP} \\
\frac{dI_M}{dt} &= \lambda_M S_H - \vartheta\lambda_P I_M - \sigma_M I_M - \pi I_M - \mu_H I_M \\
\frac{dI_P}{dt} &= \lambda_P S_H - \varepsilon\lambda_M I_P - \sigma_P I_P - \tau I_P - \mu_H I_P \\
\frac{dI_{MP}}{dt} &= \varepsilon\lambda_M I_P + \vartheta\lambda_P I_M - (\sigma_M + \sigma_P + \sigma_{MP} + \phi + \mu_H) I_{MP} \\
\frac{dS_V}{dt} &= \Lambda_V N_V - \lambda_V S_V - \mu_V S_V \\
\frac{dI_V}{dt} &= \lambda_V S_V - \mu_V I_V
\end{aligned} \tag{1}$$

Since $N_H = S_H + I_M + I_P + I_{MP}$ and $N_V = S_V + I_V$, we have

$$\begin{aligned} \frac{dN_H}{dt} &= \Lambda_H - \mu_H N_H - \sigma_M I_M - \sigma_P I_P - (\sigma_M + \sigma_P + \sigma_{MP}) I_{MP} \\ \frac{dN_V}{dt} &= (\Lambda_V - \mu_V) N_V \end{aligned} \tag{2}$$

From (2) we note that in the absence of infection $\frac{dN_H}{dt} = \Lambda_H - \mu_H N_H$, so that N_H would approach the carrying capacity $\frac{\Lambda_H}{\mu_H}$. The vector population, on the other hand, would grow exponentially for $\Lambda_V > \mu_V$, be constant for $\Lambda_V = \mu_V$ and decline for $\Lambda_V < \mu_V$.

Model (1) describes the human and mosquito populations and therefore it can be shown that the associated state variables are non-negative for all time $t \geq 0$ and that the solutions of the model (1) with positive initial data remains positive for all time $t \geq 0$ and are uniformly-bounded. We assume the associated parameters as non-negative for all time $t \geq 0$. Thus (1) is mathematically well posed and its dynamics can be considered in a proper subset Ω.

3 Equilibria Points of the Model

The steady states of the model (1) are investigated, conveniently, by first reducing the number of the variables. This is achieved by normalizing each class of the human and vector populations. Define $s_h = \frac{S_H}{N_H}$, $i_m = \frac{I_M}{N_H}$, $i_p = \frac{I_P}{N_H}$, $i_{mp} = \frac{I_{MP}}{N_H}$, $s_v = \frac{S_V}{N_V}$ and $i_v = \frac{I_V}{N_V}$ as the proportions of the classes $S_H, I_M, I_P, I_{MP}, S_V$ and I_V respectively. Let $\rho = \frac{N_V}{N_H}$, which is a constant since a mosquito takes a constant number of blood meals per unit time independent of the population density of the human host [2].

$$\begin{aligned}
\frac{ds_h}{dt} &= \frac{\Lambda_H}{N_H} - [\frac{\Lambda_H}{N_H} - \sigma_M i_m - \sigma_P i_p - (\sigma_M + \sigma_P + \sigma_{MP})i_{mp} \\
&\quad +\alpha\beta_m\rho i_v + \beta_p c(i_p + \kappa i_{mp})]s_h + \pi i_m + \tau i_p + \phi i_{mp} \\
\frac{di_m}{dt} &= \alpha\beta_m\rho i_v s_h - [\frac{\Lambda_H}{N_H} + \vartheta\beta_p c(i_p + \kappa i_{mp}) + (\sigma_M + \pi) - \sigma_P i_p \\
&\quad -\sigma_M i_m - (\sigma_M + \sigma_P + \sigma_{MP})i_{mp}]i_m \\
\frac{di_p}{dt} &= \beta_p c(i_p + \kappa i_{mp})s_h - \varepsilon\alpha\beta_m\rho i_v i_p - [\frac{\Lambda_H}{N_H} + (\sigma_M + \tau) \\
&\quad -\sigma_M i_m - \sigma_P i_p - (\sigma_M + \sigma_P + \sigma_{MP})i_{mp}]i_p \\
\frac{di_{mp}}{dt} &= \varepsilon\alpha\beta_m\rho i_v i_p + \vartheta\beta_p c(i_p + \kappa i_{mp})i_m - [\frac{\Lambda_H}{N_H} + (\sigma_M + \sigma_P + \sigma_{MP} + \phi) \\
&\quad -\sigma_M i_m - \sigma_P i_p - (\sigma_M + \sigma_P + \sigma_{MP})i_{mp}]i_{mp} \\
\frac{ds_v}{dt} &= \Lambda_V(1 - s_v) - \alpha\beta_v(i_m + \delta i_{mp})s_v \qquad (3) \\
\frac{di_v}{dt} &= \alpha\beta_v(i_m + \delta i_{mp})s_v - \Lambda_V i_v
\end{aligned}$$

and

$$\frac{dN_H}{dt} = \{\frac{\Lambda_H}{N_H} - \mu_H - \sigma_M i_m - \sigma_P i_p - (\sigma_M + \sigma_P + \sigma_{MP})i_{mp}\}N_H \qquad (4)$$

Solving (4) at an equilibrium point yields

$$\frac{\Lambda_H}{N_H} = \mu_H + \sigma_M i_m + \sigma_P i_p + (\sigma_M + \sigma_P + \sigma_{MP})i_{mp} \qquad (5)$$

We next reduce (3) to a four dimensional system by eliminating s_h and s_v, since $s_h = 1 - i_m - i_p - i_{mp}$ and $s_v = 1 - i_v$. Upon substituting (5) into the reduced system, we obtain

$$\begin{aligned}
\frac{di_m}{dt} &= \alpha\beta_m\rho i_v(1 - i_m - i_p - i_{mp}) - [\vartheta\beta_p c(i_p + \kappa i_{mp}) + \sigma_M + \pi + \mu_H]i_m \\
\frac{di_p}{dt} &= \beta_p c(i_p + \kappa i_{mp})(1 - i_m - i_p - i_{mp}) - \varepsilon\alpha\beta_m\rho i_v i_p - [\sigma_P + \tau + \mu_H]i_p \\
\frac{di_{mp}}{dt} &= \varepsilon\alpha\beta_m\rho i_v i_p + \vartheta\beta_p c(i_p + \kappa i_{mp})i_m - [\sigma_M + \sigma_P + \sigma_{MP} + \phi + \mu_H]i_{mp} \\
\frac{di_v}{dt} &= \alpha\beta_v(i_m + \delta i_{mp})(1 - i_v) - \Lambda_V i_v \qquad (6)
\end{aligned}$$

with the feasible region Ω=$\{(i_m, i_p, i_{mp}, i_v) \in \mathbf{R}_+^4 : i_m \geq 0, i_p \geq 0, i_{mp} \geq 0, i_m + i_p + i_{mp} \leq 1, 0 \leq i_v \leq 1\}$

3.1 Existence of equilibria

The equilibrium points of (6) are obtained by equating the derivatives to zero and solving for the variables. Thus, from the last equation of (6), we have

$$i_v^* = \frac{\alpha\beta_v(i_m^* + \delta i_{mp}^*)}{\alpha\beta_v(i_m^* + \delta i_{mp}^*) + \Lambda_V}$$

Suppose $i_p = i_{mp} = 0$, so that only malaria is present in the population. Equating the derivative in the first equation in (6) to zero and substituting for i_v^*, yields

$$0 = -\{\alpha^2\beta_m\beta_v\rho + \alpha\beta_v(\sigma_M + \pi + \mu_H)\}(i_m^*)^2 + \{\alpha^2\beta_m\beta_v\rho - \Lambda_V(\sigma_M + \pi + \mu_H)\}i_m^* \tag{7}$$

Solving for i_m^* from (6) gives either $i_m^* = 0$, which corresponds to a disease free equilibrium or

$$i_m^* = \frac{\alpha^2\beta_m\beta_v\rho - \Lambda_V(\sigma_M + \pi + \mu_H)}{\alpha^2\beta_m\beta_v\rho + \alpha\beta_v(\sigma_M + \pi + \mu_H)} \tag{8}$$

From (2), it is evident that at a stationary point $\Lambda_V = \mu_V$, which upon substitution in (8) yields

$$i_m^* = \frac{R_m^2 - 1}{R_m^2 + \alpha\beta_v\Lambda_V^{-1}} \tag{9}$$

where

$$R_m = \sqrt{\frac{\alpha^2\beta_m\beta_v\mu_H\Lambda_v}{\Lambda_H\mu_v^2(\sigma_M + \pi + \mu_H)}}$$

is the basic reproduction number for malaria.
We state this result in the following lemma

Lemma 3.1. *An endemic equilibrium $i_m^* > 0$ exists provided $R_m > 1$*

Suppose $i_m = i_{mp} = 0$, so that only pneumonia is present in the population. Equating the derivative in the second equation in (6) to zero and rearranging yields

$$\beta_p c(i_p^*)^2 + (\sigma_P + \tau + \mu_H)i_p^* = 0$$

from which either $i_p^* = 0$, which corresponds to the disease free equilibrium or

$$i_p^* = 1 - \frac{1}{R_p} \tag{10}$$

where

$$R_p = \frac{c\beta_p}{\tau + \sigma_P + \mu_H}$$

is the basic reproduction number for pneumonia. We state this result in the following lemma

Lemma 3.2. *An endemic equilibrium $i_p^* > 0$ exists provided $R_p > 1$*

Equating the derivative in the third equation in (6) to zero and solving for i_{mp}^* yields

$$i_{mp}^* = \frac{\varepsilon\alpha\beta_m\rho i_v^* i_p^* + \vartheta\beta_p c i_p^* i_m^*}{(\sigma_M + \sigma_P + \sigma_{MP} + \phi + \mu_H) - \vartheta\kappa\beta_p c i_m^*} \tag{11}$$

Since the state variables are taken as greater or equal to zero for $t \geq 0$, from (11) $i_{mp}^* = 0$ if and only if $i_v^* = i_m^* = i_p^* = 0$, which would be a disease free equilibrium. However, $i_{mp}^* > 0$ if $i_v^* > 0, i_m^* > 0, i_p^* > 0$, which would be an endemic equilibrium. Thus

Lemma 3.3. *An endemic equilibrium $i_{mp}^* > 0$ exists provided $R_{mp} > 1$*

Where R_{mp} is the number of secondary malaria (or pneumonia) infections due to a single malaria (or a single pneumonia-infective) individual. The basic reproduction number R_{mp} is given by

$$R_{mp} = \max\{R_m, R_p\}. \tag{12}$$

3.2 Local Stability of the Disease-Free Equilibrium

Theorem 3.4. *The disease-free equilibrium of (6) is locally stable provided $R_m < 1$ and $R_p < 1$. This implies $R_{mp} < 1$ since $R_{mp} = max\{R_m, R_p\}$.*

Proof. The local stability of the disease-free equilibrium of (6) can be studied from its Jacobian at the disease-free equilibrium. The Jacobian of (6) at the disease-free equilibrium is given by

$$J(\mathcal{E}^0) = \begin{pmatrix} -K_1 & 0 & 0 & \alpha\beta_m\rho \\ 0 & \beta_p c - (\tau + \sigma_P + \mu_H) & \kappa\beta_p c & 0 \\ 0 & 0 & -K_2 & 0 \\ \alpha\beta_v & 0 & \delta\alpha\beta_v & -\mu_v \end{pmatrix} \tag{13}$$

where $K_1 = (\sigma_M + \pi + \mu_H)$ and $K_2 = (\sigma_M + \sigma_P + \sigma_{MP} + \phi + \mu_H)$ This Jacobian has a distinct negative eigenvalue given by $-(\sigma_M+\sigma_P+\sigma_{MP}+\phi+\mu_H)$. To obtain the other eigenvalues we reduce (16) to the 3×3 block matrix A defined by

$$A = \begin{pmatrix} -(\sigma_M + \pi + \mu_H) & 0 & \alpha\beta_m\rho \\ 0 & \beta_p c - (\tau + \sigma_P + \mu_H) & 0 \\ \alpha\beta_v & 0 & -\mu_v \end{pmatrix} \tag{14}$$

The matrix A has an eigenvalue given by $\beta_p c - (\tau + \sigma_P + \mu_H)$, which may be expressed as $R_p - 1$. This eigenvalue is negative if and only if $R_p < 1$. The local stability is studied by examining the trace and determinant of of the 2×2 block matrix B defined by

$$B = \begin{pmatrix} -(\sigma_M + \pi + \mu_H) & \alpha\beta_m\rho \\ \alpha\beta_v & -\mu_v \end{pmatrix} \tag{15}$$

Clearly the trace of B is negative and its determinant is given by $det = 1 - R_m^2$. This determinant is positive if and only if $R_m < 1$. This ends the proof. □

3.3 Global Stability of the Disease-Free Equilibrium

If we consider malaria as having a higher steady state i.e $R_{mp} = R_m$, then

Theorem 3.5. *The disease-free equilibrium of (6) is globally stable provided* $R_m \leq 1$.

Proof. We may study the global stability of (6) by using the following LaSalle-Lyapunov function Consider the function defined by

$$L(i_m, i_v) = \alpha\beta_v i_m + (\sigma_M + \pi + \mu_H) i_v. \tag{16}$$

The time derivative of (16) along the solutions of (6) is given by

$$\begin{aligned} L^{'} &= \alpha\beta_v\frac{di_m}{dt} + (\sigma_M + \pi + \mu_H)\frac{di_v}{dt} \\ &= \alpha\beta_v[\alpha\beta_m\rho i_v(1-i_m) - (\sigma_M + \pi + \mu_H)i_m] \\ &\quad +(\sigma_M + \pi + \mu_H)[\alpha\beta_v i_m(1-i_v) - \mu_v i_v] \\ &= \alpha^2\beta_v\beta_m\rho i_v(1-i_m) - (\sigma_M + \pi + \mu_H)(\alpha\beta_v i_m + \mu_v)i_v \\ &\leq \frac{\alpha^2\beta_v\beta_m\mu_H\Lambda_v}{\mu_v\Lambda_H}i_v - (\sigma_M + \pi + \mu_H)\mu_v i_v \\ &\leq (\sigma_M + \pi + \mu_H)\mu_v\{\frac{\alpha^2\beta_v\beta_m\mu_H\Lambda_v}{\mu_v^2\Lambda_H(\sigma_M + \pi + \mu_H)} - 1\}i_v \\ &\leq (\sigma_M + \pi + \mu_H)\mu_v\{R_m^2 - 1\}i_v \end{aligned} \tag{17}$$

Thus $R_m \leq 1$ ensures that $L^{'} \leq 0 \ \forall \ i_m, i_v \geq 0$. Furthermore $L^{'} = 0$ whenever $R_m = 1$ and/or $i_v = 0$. LaSalle's invariance principle then implies that the disease-free equilibrium is globally stable in the interior of Ω. This completes the proof of the theorem. □

4 Effect of Treatment on Disease Course

Intervention efforts employed in malaria-endemic countries include insecticide-treated nets (ITNs), intermittent preventive treatment in pregnancy (IPTp) and infancy (IPTi) and artemisinin-based combination therapy (ACT). However, the treatment of malaria in poor resource settings, especially in the developing world, still remains a challenge. This is because of the high cost, poor disease surveillance, lack of effective diagnostic equipment, the quality of antimalarial drugs and parasite-drug resistance, poor supply and distribution chain among other reasons. There are global efforts aimed at reducing malaria mortality and burden. For example, the United States government's six-year comprehensive effort, with an investment of 63 billion US dollars, to reduce the burden of disease and promote healthy communities and families around the world called the Global Health Initiative (GHI), annonced in 2009.

To investigate the potential impact of treatment on disease progression, we carry out sensitivity analysis of the reproduction numbers.
Since children under the age of five years have not developed sufficient immunity, we consider the malaria recovery rate π as a function of treatment. Differentiating R_m partially with respect to π yields

$$\frac{\pi}{R_m}\frac{\partial R_m}{\partial \pi} = -\frac{\pi}{2(\sigma_M + \pi + \mu_H)} \tag{18}$$

The negative sign in (18) indicates that there is an expected decline in the rate of new malaria infections when malaria treatment is scaled up.
Similarly, if the pneumonia recovery rate τ is considered as a function of treatment, then

$$\frac{\tau}{R_p}\frac{\partial R_p}{\partial \tau} = -\frac{\tau}{(\sigma_P + \tau + \mu_H)} \tag{19}$$

which also suggests an expected decline in the rate of new pneumonia infections when pneumonia treatment is scaled up. In addition, an effective pneumonia vaccine would ensure that during contact of a vaccinated susceptible with an infective $\beta_p \to 0$ and hence $R_p \to 0$.

5 Numerical Simulations

5.1 The effect of pneumonia on malaria

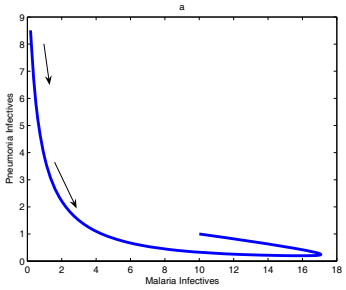

Figure 1: The effect of malaria on pneumonia

We observe from this graph that a decrease in pneumonia cases would lead to an increase in malaria cases probably due to increased mobility.

5.2 The effect of varying the co-infection recovery rate, ϕ

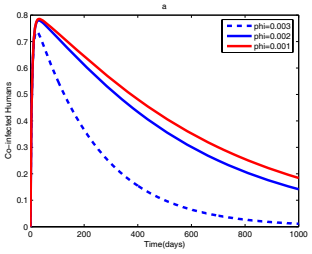

Figure 2: The effect of varying the co-infection recovery rate, ϕ

This graph shows that a higher co-infection recovery rate would lead to a reduction in co-infection cases. This makes the case for comprehensive laboratory diagnosis to rule out or confirm co-infection so that the right treatment is initiated on time.

6 Discussion

A deterministic model for the dynamics of paediatric malaria and pneumonia co-infection is presented and analysed. We establish the existence of equilibria points in terms of the basic reproduction numbers R_m and R_p. By constructing a suitable Lyapunov function, the analysis shows that the disease-free equilibrium of the model may be globally asymptotically stable whenever R_{mp} is less than unity. The health implication of this observation is that keeping the reproduction numbers below unity may be sufficient to control disease spread. To investigate the potential impact of treatment on disease progression, we carry out sensitivity analysis of the reproduction numbers. The respective analyses show that an increase in the treatment rate results in an expected decline of new disease incidences. From the numerical simulations, we deduce that a decrease in pneumonia cases would lead to an increase in malaria cases probably due to increased mobility. Furthermore, a higher co-infection recovery rate would lead to a reduction in co-infection cases. This makes the case for comprehensive laboratory diagnosis to rule out or confirm co-infection so that the right treatment is promptly initiated.

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Received: September, 2012